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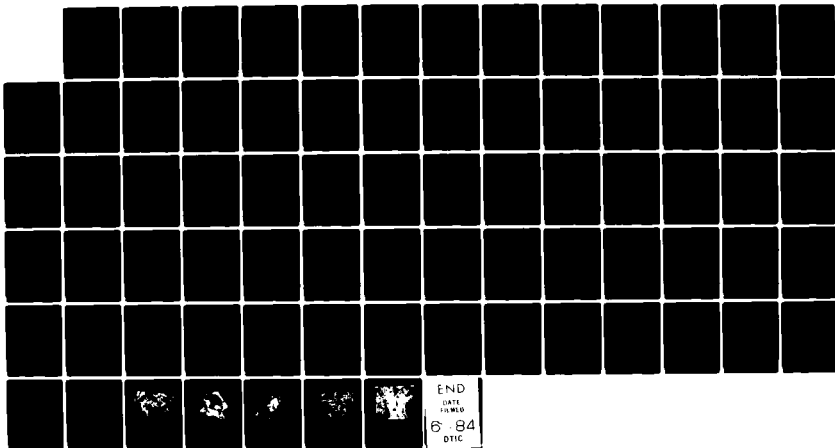
CHEMOTHERAPY OF RODENT MALARIA(U)-LONDON SCHOOL OF
HYGIENE AND TROPICAL MEDICINE (ENGLAND) DEPT OF MEDICAL
PROTOZOOLOGY W PETERS SEP 81 DAMD17-80-G-9473

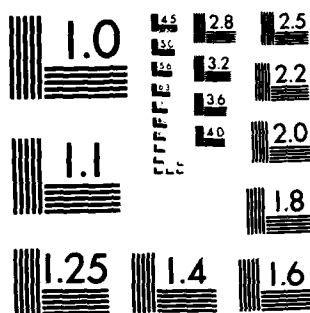
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CHEMOTHERAPY OF RODENT MALARIA

Annual/Final Report

by

WALLACE PETERS MD DSc

September 1981

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701

Contract No DAMD 17-80-G-9473

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. <i>AD A140 455</i>	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Chemotherapy of Rodent Malaria		5. TYPE OF REPORT & PERIOD COVERED Annual (2/1/81 - 9/29/81) Final (9/1/80 - 9/29/81)
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Wallace Peters, MD DSc		8. CONTRACT OR GRANT NUMBER(s) <i>JAMD17-80-G-9473</i>
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Medical Protozoology London School of Hygiene and Tropical Medicine Keppel Street, London WC1E 7HT, UK		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62770A.3M162770A871.AF.087
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command Fort Detrick, Frederick, MD 21701		12. REPORT DATE September 1981
		13. NUMBER OF PAGES 74
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		

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1. INTRODUCTION

Although an interim Annual Report was submitted at the beginning of 1981, this is the first full Annual Report submitted by the Principal Investigator from the London School of Hygiene and Tropical Medicine. Unlike the interim report, which covered only the initial four months of the contract, this report summarises the activities of the chemotherapy group for 13 months (12 months initial contract plus one month's extension). The work reported on also includes results obtained from the completion of studies commenced in Liverpool under the contracts held prior to the Principal Investigator's transfer to London.

2. ADMINISTRATIVE EVENTS

The transfer of strains of rodent malaria, referred to in the interim report, has now been completed and facilities for the investigation of the schizontocidal effect of compounds against a wide range of drug-sensitive and resistant strains of rodent malaria now exist at the School's field station at Winches Farm, St. Albans. Close liaison has been maintained by the visits of Colonel Davidson to London and of the PI to WRAIR together with several meetings between Colonel Canfield and the PI coinciding with joint service on the Steering Committee of the WHO CHEMAL Scientific Working Group.

Staff employed on US Army funds are as follows:

Emeritus Professor Dinah James (Pharmacologist)	(part time)
Senior Technologist - Mr B L Robinson (ex-Liverpool)	50% time
Trainee technician - Ms A West.	100% time

Other staff associated with this project but paid from School sources are:

Professor W Peters (PI)	20% time
Dr D C Warhurst (Biologist) (ex-Liverpool)	20% time
Dr D S Ellis (Electron Microscopist)	10% time
Dr W E Ormerod (Biologist-Pharmacologist)	20% time.

The conversion of accommodation at Winches Farm is now almost complete and insectary facilities will be available from early in 1982.

The collection of WRAIR compounds transferred from Liverpool has been supplemented by the addition of 33 compounds received from WRAIR for testing in various systems. Much of the work requiring mosquitoes has been held in abeyance pending completion of the new insectaries at Winches Farm but some studies have been undertaken as a result of the high degree of cooperation offered by colleagues in the Ross Institute of the London School and the Muséum Nationale d'Histoire Naturelle in Paris.

3. CHEMOTHERAPY STUDIES

3.1 Causal Prophylaxis

No routine causal prophylaxis tests have been run since

the submission of the interim report. Data on the compounds reported on in that report are included again in this submission and are appended as Tables 2 through 9, and summarised in Table 1.

The 5-phenoxy substituted 8-aminoquinolines WR 231530 and 232584 are both active, the former between 30 and 60 mg/kg sc and po. The latter compound is fully effective between 10 and 30 mg/kg sc and at doses greater than 30 mg/kg p.o. No residual activity (RA) was apparent at these doses. The lepidine WR 237222 is active at 30 mg/kg sc with no RA at that dose level but inactive at 30 mg/kg po. WR 225449, a Mannich base is fully active at 30 mg/kg sc and active at that dose po. RA is marked at 30 mg/kg by either route. The naphthalene methanol WR 232143 is fully active at 10 mg/kg sc with no RA and active at 30 mg/kg po with some RA. WR 218573, 7295 and 181613 display no activity sc and po at 30 mg/kg.

Assessments of residual activity have been performed on all the new WRAIR compounds received and the results of these investigations are summarised and appended as Tables 25, 26. The only compound to show marked residual activity at a dose level of 30 mg/kg sc was the floxacrine analogue WR* (BK 02771) which remained fully effective against *P.y.nigeriensis* challenge seven days after treatment and was still partially effective, producing delay in the development of infection, 21 days after treatment.

At a dose level of 100 mg/kg sc the Mannich base WR 194965 was fully effective two days post treatment and marked activity was apparent seven days post treatment. Marked residual activity two days after treatment was shown at 100 mg/kg sc by WR 238605 but seven days after treatment no effect remained. The 8-aminoquinoline WR 232584 was also checked for residual activity and the test confirmed that there was no residual activity at the MFAD (30 mg/kg sc) although slight residual activity was present at 100 mg/kg sc.

The 8-aminoquinoline WR 225448 has been examined in the rat model developed by Dr Irène Landau (see section 3.7) (Table 27) and has shown to have a direct effect on the EE schizont.

3.2 Gametocytocidal action

No routine gametocytocidal screening has been carried out but a number of compounds are scheduled for examination as soon as the Winches Farm insectaries are functioning.

3.3 Blood schizontocides

Data obtained with WRAIR compounds in our blood schizontocidal "four-day test" system with sensitive and drug resistant lines are presented in Tables 11 through 24, and summarised in Table 10. In particular we note that the Mannich base WR 194965 is highly active sc against the N strain and the moderately chloroquine resistant RC strain. The other Mannich base WR 228258 is somewhat less active sc but more active po against the N strain and shows a slight but significant loss of activity against the mefloquine resistant N/1100 strain. The 8-aminoquinolines WR 225448, 232584 and 226296 are highly effective against the N strain. While WR 232584 and 225448 are only slightly less active against the primaquine resistant P line, WR 226296

*WR No. requested

is much less effective against this line.

Floxacrine and the two floxacrine analogues WR* (BKO2771) and WR* (BK 02780) have been compared and, whilst both analogues are markedly less active than floxacrine, it is interesting to note that all three compounds are more active against the N/1100 line than against N strain and that both floxacrine and WR* (BKO2771) are also significantly more active against NS strain than N strain.

3.4 Sporontocidal action

The absence of suitable insectary facilities has prevented the establishment of a routine screen. However, it has been possible to examine one compound, WR 228258, so far. No sporontocidal action is shown by this compound.

Routine screening for sporontocidal effect is scheduled to begin in early 1982.

3.5 Drug combinations

No studies are currently being made.

3.6 Development and prevention of drug resistance

A long term study is being run of the effects of administering a mixture of mefloquine with "Fansidar" (pyrimethamine + sulfadoxine)* using the relapse technique i.e. fixed, single drug dose at the time of infection. To date, resistance to mefloquine would appear to be inhibited by the simultaneous administration of "Fansidar" when compared with earlier studies on the development of resistance to mefloquine alone. Our initial results are shown graphically in Figure 1 (a) and 1 (b) and would tend to support the claims of Merkli et al (1980) that resistance develops to mefloquine more slowly when it is given together with Fansidar. Further work on this is being carried out and, currently, we are studying the development of mefloquine resistance in a line which is already resistant to Fansidar. No data are as yet available on this line.

3.7 Mode of drug action

The main emphasis of our work on mode of action has been directed towards the two Mannich bases WR 228258 and 194965 and the 8-aminoquinoline WR 225448. The techniques employed so far have been the chloroquine included pigment clumping test (CIPC) and the Desjardin H³ hypoxanthine incorporation test (HIT). These in vitro techniques utilise P. berghei (CIPC) and the Wellcome-Liverpool strain of P. falciparum (HIT). Additionally, ultrastructural studies on the effects of these compounds in vivo against P. berghei have been undertaken.

(i) P. berghei CIPC

WR 194965 does not induce clumping but will inhibit competitively clumping produced by chloroquine. The dissociation constant (K_1) at the clumping receptor

*WR No. requested

is 80 nmol/l compared to 20 nmol/l for chloroquine and 410 nmol/l for quinine. The slope (n) is 1.7 compared to 2.3 for quinine and 1.0 for mefloquine.

WR 228258 induces pigment clumping which is competitively inhibited by quinine. k_i at the clumping receptor is 372 nmol/l.

WR 225448 neither induces nor inhibits clumping.

- (ii) P. falciparum in vitro microtest using Desjardin et al technique of H^3 hypoxanthine incorporation.

WR 194965	IC ₅₀	= < 1.95 nmol/l	} Preliminary results
WR 228258	IC ₅₀	= ~ 1.95 nmol/l	
WR 225448	IC ₅₀	= 252 nmol/l	

- (iii) Ultrastructural changes

The following is a summary of the main ultrastructural changes in P. berghei blood stages in vivo following administration of 10 mg/kg x 1 sc.

WR 194965 one of the first effects (apparent by 3 hours) is swelling of the digestive vacuoles, and this is followed by the release of some pigment into the cytoplasm. Some mitochondrial swelling occurs..

WR 228258 Although there is some clumping of pigment at high doses, this is not a major feature of the changes in vivo. Digestive vacuoles swell, nuclear blebbing is apparent at 30 minutes and there is general membrane damage.

WR 225448 After 1 to 3 hours, mitochondrial proliferation is found.

- (iv) Comments

WR 194965 The activity in the clumping test indicates reaction with the digestive vacuoles (possibly via haemin interactions) and this is confirmed by the electron microscopy results. The k_i for clumping inhibition and the IC₅₀ for P. falciparum differ by a factor of 40 which could be accounted for by the short term nature of the CIPC as compared with the prolonged HIT. Also interspecific differences may be involved.

WR 228258 The major observation here is the difference between clumping test results and the results of the P. falciparum study together with the in vivo P.berghei study. The clumping k_m and the incorporation IC₅₀ differ by a factor of 186. In addition the studies in vivo showed that clumping was not produced at therapeutic concentrations and that nuclear changes were evident early in the time course.

This indicates that the therapeutic action of the drug depends on a different mode of action from that of chloroquine. The difference between short term P.berghei and long term P.falciparum results in vitro

together with these discrepant in vivo results, suggest that an active metabolite, possibly with anti-nuclear activity, may be involved.

WR 225448 The inactivity in the clumping system and the development of swollen mitochondria followed by mitochondrial proliferation, point to a typical 8-amino-quinoline-like activity. The activity in the long term in vitro test on P.falciparum, although lower (IC_{50} of 252 nmol/l) than that of WR 194965 and 228258, indicates that some production of the active metabolite may be occurring in vitro.

In conclusion, WR 194965 and 228258 appear to have novel modes of action. The apparent anti-nuclear activity of WR 228258 suggests that special attention should be given to its effects on the bone marrow and other actively dividing cells when animal toxicity studies are carried out.

WR 225448 has primaquinelike effects and may be expected to have some lytic effects on G6PD deficient erythrocytes. The three drugs may be expected to have activity against chloroquine - resistant malarias.

Electron micrographs illustrating some of the effects of these compounds appear as Plates 1, 2 and 3.

(v) Ultrastructural effects on EE schizonts

Preliminary electron microscope studies on the effects of primaquine and WR 225448 in P.y.nigeriensis sporozoite infected rats have yielded the following results.

1. Primaquine causes thickening and presumably malfunction of mitochondria.
2. WR 225448 produces a primaquine-like effect on mitochondria.
3. WR 225448 also appears to prevent transport of "enzyme-containing lysosomes" from the periphery of the schizont into the host cell.
4. WR 225448 may exert a toxic effect on the hepatocytes themselves.

Some of the effects of a single sc dose of 50 mg/kg of primaquine and 1.0 mg/kg of WR 225448 on the exoerythrocytic schizonts of P.y.nigeriensis are shown in Plates 4 and 5.

3.8 Development of new techniques

The technique for producing high levels of EE schizonts of P.y.nigeriensis developed by Dr. Irene Landau in Paris has been examined and appears to be a very suitable basis for the development of a test for true causal prophylactic activity

and also for anti-sporozoite effects of compounds. The commissioning of the new Winches Farm insectaries will allow us to examine this subject in detail and produce a test suitable for routine screening.

A recent visit to the school in London by Dr. Michael Hollingdale drew our attention to the in vitro foetal lung system for the cultivation of rodent malaria. This would appear to hold possibilities for the study of effects of compounds on EE stages in vitro and it is planned to investigate this in more detail.

Preliminary studies on the use of the Duke's mini-feeder have been carried out and we have succeeded in transmitting P.y.nigeriensis to Anopheles stephensi with this equipment. Further studies, including the use of gametocyte producing lines of P.falciparum in culture, are planned.

It is felt that the development of a model for the investigation of the hypnozoite stage, responsible for relapse in P. cynomolgi and, probably also, P. vivax and P. ovale is of great importance and to this end, we intend to examine a number of parasites for suitability.

4.0 PAPERS PUBLISHED

4.1 Already published

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Peters, W. (1982) Antimalarial drug resistance: an increasing problem, British Medical Bulletin. 38

Warhurst, D.C., Robinson, B.L. and Peters, W. Antimalarial activity of erythromycin against Plasmodium knowlesi (1982) Ann.trop.Med.

Warhurst, D.C. and Gould, S., The activity of chloroquine and related blood schizontocides and of some analogues in drug-induced pigment clumping (1982) Ann.trop.Med. Parasit.

5. APPENDICES

- 5.1 Summary of causal prophylactic test data (Table 1)
- 5.2 Individual causal prophylactic test reports (Tables 2-9)
- 5.3 Summary of blood schizontocidal (4 day test) data (Table 10)
- 5.4 Individual blood schizontocidal (4 day test) reports
(Tables 11-24)
- 5.5. Summary of residual activity tests (Tables 25, 26)
- 5.6 Effects of WR 225448 in rat test for EE activity (Table 27)
- 5.7 Comparison of development of resistance to mefloquine
(alone and administered with Fansidar) in P.berghei (Fig 1a, 1b)
- 5.8 Electron micrographs showing effects of WR 194965, 228258
and 225448 against blood stages of P.berghei (Plates 1-3)
- 5.9 Electron micrographs showing effects of primaquine and
WR 225448 against EE stages of P.y.nigeriensis (Plates 4,5)

SUMMARY OF CAUSAL PROPHYLACTIC TEST DATA

WR No.	LIV. No.	Minimum Fully active dose (mg/kg x l)	Residual action at active dose	COMMENT	Type of Compound
BG 94916	1533	30-60 s.c.		Preliminary data	8-aminoquinoline
BG 94916	1533	30-60 p.o.		Preliminary data	"
BH 57098	1613	> 30 s.c.	Nil at 30	Active at 30 s.c.	"
BH 57098	1613	-	-	Inactive at 30 p.o.	"
BH 05361	1541	10-30 s.c.	Nil at 30	Fully active at 30 s.c.	"
BH 05361	1541	> 30 p.o.	Nil at 30	Active at 30 p.o.	"
BE 66994	1543	-	-	Inactive at 30 s.c.	"
BE 66994	1543	-	-	Inactive at 30 p.o.	"
BB 49961	1556	-	-	Inactive at 30 s.c.	Hydroxyquinoline
BB 49961	1556	-	-	Inactive at 30 p.o.	"
BG 62110	1557	-	-	Inactive at 30 s.c.	Quinoline Methanol
BG 62110	1557	-	-	Inactive at 30 p.o.	"
BG 94925	1534	10-30 s.c.	Marked at 30	Fully active at 30 s.c. - all activity residual	Mannich base
BG 94925	1534	> 30 p.o.	Marked at 30	Active at 30 p.o. - all activity residual	"
BH 01069	1542	3-10 s.c.	Nil at 10	Fully active at 10 s.c.	Naphthalene
BH 01069	1542	> 30 p.o.	Present at 30	Active at 30 p.o. - Some residual activity	"

CAUSAL PROPHYLAXIS TEST NO: BR 741

DRUG: 8-aminoquinolines IV/1533

WR 231530AA

DATE:

BOTTLE NO. BG94916

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION:

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ⁰	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	Residual Activity		
0	5/5		5/5	5.55		3.67					
30.0	2/3			>8.91							ACTIVE
60.0	0/3			>14							FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

30-60

RESIDUAL ACTIVITY

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DATE:

DRUG: 8-aminoquinoline LIV/ 1533

WR 231530AA

BOTTLE NO. BG94916

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: po

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE				GMP 2&P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	(b - a)	Residual Activity		
0	5/5		5/5	5.55		3.67						
30.0	2/3			10.39								ACTIVE
60.0	0/3			14								FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE.....30-60.....mg/kg

RESIDUAL ACTIVITY

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DRUG: 8-aminoquinoline LIV/ 1613

WR 237222AA

DATE:

BOTTLE NO. BH 57098

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION:

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: N13

DOSE mg/kg	PATENCY RATE			GMP 2&P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ⁰	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	(b - a)		
0	5/5	3/3	5/5	5.55	3.65	3.67					
1.0	3/3			5.34						NIL	INACTIVE
3.0	3/3			5.74						NIL	INACTIVE
10.0	3/3		3/3	5.02		3.73				NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 10 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

STRAIN: NIG

[illegible]

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DRUG: 8-aminoquinoline_{LIV}/ 1613

WR 237222 AA

DATE:

BOTTLE NO. BH 57098

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: PO

TIME AFTER INFECTION:

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2&P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ⁰	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	Residual Activity		
0	5/5	3/3	5/5	5.55	3.65	3.67					
3.0	3/3			5.38						NIL	INACTIVE
10.0	3/3			5.53						NIL	INACTIVE
30.0	3/3		3/3	5.54		3.74			NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 720

DRUG: 8-aminoquinoline LIV/1541

WR 232584 AA

DATE:

BOTTLE NO. BH 05361

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: SC

TIME AFTER INFECTION: 2Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2*P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ^c	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	Residual Activity		
0	5/5	3/3	5/5	5.57	4.45	4.50					
3.0	3/3			6.17						NIL	
10.0	1/3			11.27						> 5.70	ACTIVE
30.0	0/3		3/3	14		4.82			NIL	> 8.43	FULLY ACTIVE

MINIMUM FULLY ACTIVE DOSE.....10-30.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO:

BR 720

DATE:

DRUG: 8-aminoquinoline LIV/ 1541

WR 232584 AA

BOTTLE NO. BH 05361

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: po

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: N1g

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f) (b - a) (e - a) - (b - a) (c - a)	Residual Activity			
0	5/5	3/3	5/5	5.57	4.45	4.50					
3.0	3/3			5.80					NIL		INACTIVE
10.0	3/3			5.95					NIL		INACTIVE
30.0	2/3		3/3	8.53		4.39		NIL	> 2.96		ACTIVE

MINIMUM FULLY ACTIVE DOSE.....^{>30}.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728

DATE:

DRUG: 8-aminoquinoline LIV/ 1543

WR 218573AA

BOTTLE NO. BE66994

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: SC

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: N13

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ⁰	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	(b - a)(e - a) (c - a)	Residual Activity		
0	5/5	3/3	5/5	4.94	3.80	3.92					
3.0	3/3			5.03						NIL	INACTIVE
10.0	3/3			5.17						NIL	INACTIVE
30.0	3/3		3/3	5.28		3.87			NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY

NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO:

BR 728

DATE:

DRUG: 8-aminoquinoline LIV/ 1543

WR 218573AA

BOTTLE NO. BE66994

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: po

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2AP			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^c	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	Residual Activity		
0	5/5	3/3	5/5	4.94	3.80	3.92					
3.0	3/3			5.18						NIL	INACTIVE
10.0	3/3			5.25						NIL	INACTIVE
30.0	3/3		3/3	6.19		3.86			NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742

DRUG: Hydroxyquinoline LIV/ 1556

WR 7295AD

DATE:

BOTTLE NO. BB49961

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION:

SC

TIME AFTER INFECTION: 2 Hrs-

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NiG

DOSE mg/kg	PATENCY RATE			GMP 2 nd P			(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)} - (b - a)$		
0	5/5	3/3	5/5	5.27	4.00	3.82				
3.0	3/3			5.13					NIL	INACTIVE
10.0	3/3			5.96					NIL	INACTIVE
30.0	3/3			5.13		3.76			NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742

DRUG: Hydroxyquinoline_{IV}/ 1556

WR 7295AD

DATE:

BOTTLE NO. BB49961

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: PO

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: N13

DOSE mg/kg	PATENCY RATE			GMP 28P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ⁰	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$ - (b - a)	Residual Activity		
0	5/5	3/3	5/5	5.27	4.00	3.82					
3.0	3/3			4.73						NIL	INACTIVE
10.0	3/3			4.92						NIL	INACTIVE
30.0	3/3		3/3	5.49		3.60			NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 P.O.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742

DRUG: Quinoline
Methanol

LIV/ 1557

WR 181613 AB

BOTTLE NO. BG62110

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: sc

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE				GMP 24P			(a = 2) ACTIVITY VALUES		Prophylactic Activity	COMMENT
	C ⁰ / T ₀	XC	C ^x / T _x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	Residual Activity		
0	5/5	3/3	5/5	5.27	4.00	3.82					
3.0	3/3			5.66						NIL	INACTIVE
10.0	3/3			5.01						NIL	INACTIVE
30.0	3/3		3/3	5.95		3.95			NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 742

DATE:

DRUG: Quinoline
Methanol

LIV/ 1557

WR 181613 AB

BOTTLE NO. BG 62110

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: po

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: N13

DOSE mg/kg	PATENCY RATE			GMP 28P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	Residual Activity		
0	5/5	3/3	5/5	5.27	4.00	3.82					
3.0	3/3			4.90						NIL	INACTIVE
10.0	3/3			4.59						NIL	INACTIVE
30.0	3/3			5.04		3.70			NIL	NIL	INACTIVE

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY NIL AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DATE:

DRUG: Mannich Base LIV/ 1534 WR 225449 AB

BOTTLE NO. BG 94925

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: SC

TIME AFTER INFECTION: 2 Hrs

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: N13

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ⁰ / T ⁰	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b-a)(e-a)}{(c-a)}$	(b - a)	Residual Activity	
0	5/5	3/3	5/5	5.55	3.65	3.67					
3.0	2/3			5.24							
10.0	3/3		3/3	5.09		5.26	-0.46 - $\left[\frac{1.65 \times 3.26}{1.67} - 1.65 \right]$			1.58	INACTIVE
30.0	0/3		2/3	>14		12.10	>8.45 $\left[\frac{1.65 \times 10.10}{1.67} - 1.65 \right]$			8.34	FULLY ACTIVE-ALL ACTIVITY RESIDUAL

MINIMUM FULLY ACTIVE DOSE.....10-30.....mg/kg

RESIDUAL ACTIVITY MARKED AT 30 mg/kg x 1 s.c.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 741

DRUG: Mannich Base LIV/ 1534 WR 225449 AB

PREPARATION: Tween 80/H₂O

VERTEBRATE HOST: TFW MICE

ROUTE OF ADMINISTRATION: po

PARASITE (SUB) SPECIES: P. y. nigeriensis

DATE:

BOTTLE NO. BG94925

TIME AFTER INFECTION: 2 Hrs.

STRAIN: N13

DOSE mg/kg	PATENCY RATE			GMP 28P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	(b - a)	Residual Activity	
0	5/5	3/3	5/5	5.55	3.65	3.67					
10.0	3/3		3/3	6.42		3.79	0.87 -			NIL	INACTIVE
30.0	3/3		3/3	10.75		8.82	$5.20 - \left[\frac{1.65 \times 6.82}{1.67} - 1.65 \right]$			5.09	RESIDUAL ACTIVITY ONLY

MINIMUM FULLY ACTIVE DOSE.....mg/kg
> 30

RESIDUAL ACTIVITY MARKED AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728

DATE:

DRUG:Naphthalene

LIV/ 1542

WR 232143AA

BOTTLE NO. BH 01069

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: SC

2 Hrs.

TIME AFTER INFECTION:

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE			GMP 2%P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b-a)(e-a)}{(c-a)}$ - (b - a)	Residual Activity		
0	5/5		5/5	4.94	3.80	3.92					
3.0	2/3			>8.01		3.86			NIL	> 3.07	SLIGHTLY ACTIVE
10.0	0/3			>14		4.65			NIL	> 9.06	FULLY ACTIVE
30.0	0/3			>14		8.76	$> 9.06 - \left[\frac{1.80 \times > 6.76}{1.92} - 1.80 \right]$		> 4.54	> 7.36	FULLY ACTIVE-SOME RESIDUAL ACTIVITY

MINIMUM FULLY ACTIVE DOSE.....3-10.....mg/kg

RESIDUAL ACTIVITY NIL AT 10 mg/kg x 1 s.c.

PRESENT AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

CAUSAL PROPHYLAXIS TEST NO: BR 728

DATE:

DRUG: Naphthalene LIV/ 1542

WR 232143AA

BOTTLE NO. BH 01069

PREPARATION: Tween 80/H₂O

ROUTE OF ADMINISTRATION: po

TIME AFTER INFECTION: 2 Hrs.

VERTEBRATE HOST: TFW MICE

PARASITE (SUB) SPECIES: P. y. nigeriensis

STRAIN: NIG

DOSE mg/kg	PATENCY RATE				GMP 2&P			(a = 2) ACTIVITY VALUES			Prophylactic Activity	COMMENT
	C ^o / T ^o	XC	C ^x / T ^x	f/h	b	c/e	(h - f)	$\frac{(b - a)(e - a)}{(c - a)}$	(b - a)	Residual Activity		
0	5/5	3/3	5/5	4.94	3.80	3.92						
3.0	3/3			5.38		3.83				NIL	NIL	
10.0	2/3			8.08		3.96				NIL	> 3.14	SLIGHTLY ACTIVE
30.0	1/3		3/3	11.00		7.65	$> 6.06 - \left[\frac{1.80 \times 5.65}{1.92} - 1.80 \right]$			3.50	> 2.56	ACTIVE-SOME RESIDU ACTIVITY

> 30

MINIMUM FULLY ACTIVE DOSE.....mg/kg

RESIDUAL ACTIVITY PRESENT AT 30 mg/kg x 1 p.o.

PRINCIPAL INVESTIGATOR: PROFESSOR W. PETERS

SUMMARY OF BLOOD SCHIZONTOCIDAL (4 DAY TEST) DATA

L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED 50	ED 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90	ED 90	I 90
1541	WR 232584 BH 05361	sc	0.3	0.5	1.9	3.8	0.4	0.8	2.1	4.2								
		po	0.4	0.6	3.2	5.3	0.9	1.5	2.6	4.3								
1391	WR 226296 BG 44452	sc	0.5	1.2	1.9	1.6	0.6	0.5	26.0	21.7								
		po	0.3	0.5	2.9	5.8	0.7	1.4	7.8	15.6								
LON No.																		
1707	WR 194965AG BG 56327	sc	2.2	3.8	4.2	1.1	> MTD	-										
1708	WR 228258AH BJ 30663	sc	4.0	10.0													26.0	2.6
		po	1.2	2.4													18.0	7.9
1709	WR 225448AG BH 58522	sc	0.2	0.3	0.8	2.7	0.4	1.3	1.2	4.0							0.4	1.3
		po	0.1	0.2	0.6	3.0	0.6	3.0	1.2	6.0								

ED₅₀ / ED₉₀ = mg/kg x 4 MTD = maximum tolerated dose

SUMMARY OF BLOOD SCHIZONTICIDAL (4 DAY TEST) DATA

LON/ L I V No.	Suppliers No.	Route	N		NS		RC		P		B		PYR		ORA		N/1100	
			ED	50	ED	90	ED	90	I	ED	90	I	ED	90	I	ED	90	I
LIV 1307	WR 182232AC BE 08456	sc po		3.2	7.3													
LIV 1354	WR 194343 BC 06452	sc po		1.5	4.2													
LIV 1381 LON 1722	WR 215295 BE 16378	sc po		4.6	11.0													
LIV 1382	WR 216100 BE 17491	sc po		2.1	5.6													
LIV 1542	WR 232143 BH 01069	sc		16.5	50.0													
LIV 1528	Floxacin	SC		0.7	3.0	0.8	0.3										1.3	0.4
LON 1752	BK 02771	sc		3.0	84.0	25.0	0.3										46.0	0.5

ED₅₀ / ED₉₀ = mg/kg x 4 MTD = maximum tolerated dose

[illegible]

$ED_{50} / ED_{90} = \text{mg/kg} \times 4$ $MTD = \text{maximum tolerated dose}$

SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 11a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 232584
 or NUMBER BHO5361
 LIV/1541..... PARASITE (SUB) SPECIES...P.b.berghei.....
 Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.3	5		-	53.5 \pm 5.0
	1.0	5			0
	3.0	5	1	-	0
	10.0	5		-	0
	\emptyset	10		42.6	
ED ₅₀ (range)	0.3(0.2-0.4)				
ED ₉₀ (range)	0.5(0.4-0.6)				
	Resistance factor 90 1.0				
NS	0.3	5		-	78.7 \pm 2.8
	1.0	5		-	67.1 \pm 2.4
	3.0	5	1	-	2.1 \pm 1.2
	10.0	5		-	0
	\emptyset	10		48.3	
ED ₅₀ (range)	0.8(0.5-1.4)				
ED ₉₀ (range)	1.9(1.1-3.2)				
	Resistance factor 90 3.8				

LONDON SCHOOL OF
 HYGIENE & TROPICAL
 MEDICINE

DATE...5th January 1982... PRINCIPAL PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 11b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 232584
 or NUMBER BH 05361
 LIV/1541.....

PARASITE (SUB) SPECIES. *P.b.berghei*.....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
RC	0.3	5		-	17.2 \pm 11.0
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	\emptyset	10		3.5	
ED ₅₀ (range)	0.2(0.1-0.3)				
ED ₉₀ (range)	0.4(0.3-0.5)				
	Resistance Factor 90 0.8				
P	0.3	5		-	67.2 \pm 4.1
	1.0	5		-	61.3 \pm 5.7
	3.0	5	1	-	28.1 \pm 5.7
	10.0	5		-	0
	\emptyset	10		23.5	
ED ₅₀ (range)	1.0(0.4-2.2)				
ED ₉₀ (range)	2.1(0.7-4.7)				
	Resistance factor ₉₀ 4.2				

LONDON SCHOOL OF
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DATE...5th January 1962.....

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PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 11c

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 232584
 BH 05361
 LIV/1541
 PARASITE (SUB) SPECIES..P.b.berghai.....
 Route of administration : P.O.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.3	5		-	71.8 ± 3.6
	1.0	5		-	1.9 ± 0.9
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		42.6	
ED ₅₀ (range)	0.4 (0.3-0.4)				
ED ₉₀ (range)	0.6 (0.5-0.8)				
	Resistance factor 90 1.0				
	0.3	5		-	76.6 ± 2.0
	1.0	5		-	75.0 ± 4.4
	3.0	5	1	-	46.8 ± 7.6
	10.0	5		-	0
	Ø	10		48.3	
ED ₅₀ (range)	1.9 (1.1-3.0)				
ED ₉₀ (range)	3.2 (1.9-5.1)				
	Resistance factor 90 5.3				

LONDON SCHOOL OF
 HYGIENE & TROPICAL
 MEDICINE

DATE.....5th January 1982.....

PRINCIPAL

PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 11d

WR 232584

(BLOOD SCHIZONTOCIDES)

BH 05361

COMPOUND NAME
or NUMBER

LIV/1541

PARASITE (SUB) SPECIES..... P.b.berghei

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	0.3	5		-	51.4 \pm 16.5
	1.0	5		-	40.0 \pm 16.5
	3.0	5	1	-	0
	10.0	5		-	0
	\emptyset	10		3.5	
ED ₅₀ (range)	0.5(0.2-1.0)				
ED ₉₀ (range)	0.9(0.5-1.8)				
	Resistance factor 90 ^{1.5}				
P	0.3	5		-	78.3 \pm 2.5
	1.0	5		-	66.4 \pm 5.7
	3.0	5	1	-	51.1 \pm 3.3
	10.0	5		-	0
	\emptyset	10		23.5	
ED ₅₀ (range)	1.3(0.5-3.3)				
ED ₉₀ (range)	2.6(0.9-6.2)				
	Resistance factor 90 ^{4.3}				

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MEDICINE

DATE..... 5th January 1982

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 12a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 226296
 or NUMBER BH 44452
 LIV/1391..... PARASITE (SUB) SPECIES P.b.berghei.....

Route of administration : S.C.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.3	5		-	69.0 ± 2.7
	1.0	5		-	4.2 ± 1.8
	3.0	5	1	-	2.1 ± 0.9
	10.0	5		-	0
	Ø	10		42.6	
ED ₅₀ (range)	0.5(0.2-0.6)				
ED ₉₀ (range)	1.2(0.6-1.8)				
	Resistance factor 90 1.0				
NS	0.3	5		-	71.2 ± 2.8
	1.0	5		-	66.3 ± 3.6
	3.0	5	1	-	15.3 ± 5.6
	10.0	5		-	
	Ø	10		48.3	
ED ₅₀ (range)	0.8(0.4-1.7)				
ED ₉₀ (range)	1.9(1.0-4.0)				
	Resistance factor 90 1.6				

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 MEDICINE

DATE... 5th January 1982

PRINCIPAL

PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 12b

(BLOOD SCHIZONTOCIDES)

WR 226296
 BH 44452
 COMPOUND NAME
 or NUMBER LIV/L391..... PARASITE (SUB) SPECIES...P.b.berghei.....
 Route of administration : sc

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR}\%}{\text{Control PR}\%} \times 100$
RC	0.3	5		-	91.4 ± 27.4
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	\emptyset	10		3.5	
ED ₅₀ (range)	0.4(0.3-0.7)				
ED ₉₀ (range)	0.6(0.4-0.9)				
	Resistance factor ₉₀ 0.5				
P	0.3	5		-	95.3 ± 4.9
	1.0	5		-	87.7 ± 3.3
	3.0	5	1	-	75.8 ± 7.4
	10.0	5		-	32.3 ± 6.5
	\emptyset	10		23.5	
ED ₅₀ (range)	4.6(1.8-10.0)				
ED ₉₀ (range)	26 (10-56)				
	Resistance factor ₉₀ 21.7				

LONDON SCHOOL OF
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DATE.....5th January 1982.....

PRINCIPAL

PROF.W. PETERS

SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 12c

WR 226296

(BLOOD SCHIZONTOCIDES)

BH 44452

COMPOUND NAME LIV/1391

P.b.berghei

or NUMBER

..... PARASITE (SUB) SPECIES.....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% $\times 100$
N	0.3	5		-	54.5 + 7.8
	1.0	5		-	0
	3.0	5	1	-	0
	10.0	5		-	0
	\emptyset	10		48.3	
ED ₅₀ (range)	0.3(0.2-0.4)				
ED ₉₀ (range)	0.5(0.4-0.6)				
	Resistance factor 90 1.0				
NS	0.3	5		-	73.7 \pm 2.4
	1.0	5		-	72.1 \pm 3.2
	3.0	5	1	-	19.5 \pm 5.2
	10.0	5		-	0
	\emptyset	10		48.3	
ED ₅₀ (range)	1.6(1.2-2.2)				
ED ₉₀ (range)	2.9(2.2-4.0)				
	Resistance factor 90 5.8				

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DATE..... 5th January 1982

PRINCIPAL

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 12d

WR 226296

(BLOOD SCHIZONTOCIDES)

BH 44452

COMPOUND NAME
or NUMBER

LIV/1391

PARASITE (SUB) SPECIES... *P. b. berghei*.....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	0.3	5		-	34.3 ± 11.0
	1.0	5		-	11.4 ± 5.5
	3.0	5	1	-	0
	10.0	5		-	0
	Ø	10		3.5	
ED ₅₀ (range)	0.3(0.2-0.6)				
ED ₉₀ (range)	0.7(0.4-1.2)				
	Resistance factor 90 1.4				
P	0.3	5		-	61.3 ± 7.4
	1.0	5		-	58.7 ± 2.5
	3.0	5	1	-	51.9 ± 4.1
	10.0	5		-	8.5 ± 3.3
	Ø	10		23.5	
ED ₅₀ (range)	1.4(0.4-3.8)				
ED ₉₀ (range)	7.8(2.0-22.0)				
	Resistance factor 90 15.6				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 13a

WR 194965 AG

(BLOOD SCHIZONTOCIDES)

BG 56327

P.berghei

COMPOUND NAME LON 1707

or NUMBER

.....

PARASITE (SUB) SPECIES.....

Route of administration : S.C.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	1.0	5		-	95.0 \pm 3.0
	3.0	5		-	39.0 \pm 6.2
	10.0	5	1	-	0
	\emptyset	10		53.0	
ED ₅₀ (range)	2.2(1.8-2.8)				
ED ₉₀ (range)	3.8(3.1-4.7)				
	Resistance factor 90 1.0				
NS	1.0	5		-	98.0 \pm 3.6
	3.0	5		-	40.0 \pm 5.6
	10.0	5	1	-	0.05 \pm 0.05
	30.0	5		-	0
	\emptyset	10		46.0	
ED ₅₀ (range)	2.4(1.9-3.0)				
ED ₉₀ (range)	4.2(3.2-5.0)				
	Resistance factor 90 1.1				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 13b

WR 194965
 BG 56327
 LON 1707
 COMPOUND NAME
 or NUMBER

(BLOOD SCHIZONTOCIDES)
 P.berghei
 PARASITE (SUB) SPECIES.....
 Route of administration : S.C.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	3.0	5		-	98.5 ± 4.5
	10.0	5		-	95.0 ± 3.2
	30.0	5	1	-	84.0 ± 4.3
	100.0	5		-	> LD 100
	\emptyset	10		6.2	
ED ₅₀ (range)	> MTD				
ED ₉₀ (range)	>> MTD				
	Resistance factor ₉₀				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistance factor ₉₀				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 14a

WR 228258

(BLOOD SCHIZONTOCIDES)

BJ 30663

COMPOUND NAME
or NUMBER

LON 1708

PARASITE (SUB) SPECIES..... P.berghei

Route of administration : S.C.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	1.0	5		-	95.3 ± 5.9
	3.0	5		-	83.6 ± 7.7
	10.0	5	1	-	7.8 ± 3.6
	30.0	5		-	0.2 ± 0.1
	\emptyset	10		37.6	
ED ₅₀ (range)	4.0(2.6-6.7)				
ED ₉₀ (range)	10.0 (7.0-17.0)				
	Resistance factor 50 1.0				
N/1100	1.0	5		-	85.0 ± 10.0
	3.0	5		-	51.3 ± 15.9
	10.0	5	2	-	39.0 ± 5.2
	30.0	10		-	33.1 ± 5.4
	100.0	5		-	0
	\emptyset	10		17.7	
ED ₅₀ (range)	13.0(7.5-23.0)				
ED ₉₀ (range)	26.0(15.0-44.0)				
	Resistance factor 90 2.6				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 14b

WR 228258AH

(BLOOD SCHIZONTOCIDES)

BJ 30663

COMPOUND NAME LON 1708

P.berghei

or NUMBER

PARASITE (SUB) SPECIES.....

Route of administration : P.O.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
N	1.0	5		-	54.0 \pm 15.0
	3.0	5		-	15.4 \pm 11.2
	10.0	5	1	-	0
	Ø	10		37.6	
ED ₅₀ (range)	1.2(0.9-1.7)				
ED ₉₀ (range)	2.4(1.0-3.4)				
	Resistance factor 90 1.0				
N/1100	1.0	5		-	88.4 \pm 7.2
	3.0	5		-	56.3 \pm 6.9
	10.0	5	2	-	49.1 \pm 11.4
	30.0	10		-	27.9 \pm 9.0
	100.0	5		-	0
	Ø	10		17.7	
ED ₅₀ (range)	9.5(4.4-24.0)				
ED ₉₀ (range)	18.0(8.0-40.0)				
	Resistance factor 90 7.9				

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TABLE 15a

WR 22448AG (BLOOD SCHIZONTOCIDES)
 BH 58522
 COMPOUND NAME LON 1709 P.berghei
 or NUMBER PARASITE (SUB) SPECIES.....
 Route of administration : S.C.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.1	5		-	87.5 ± 5.2
	0.3	5		-	4.5 ± 1.0
	1.0	5	1	-	0
	3.0	5		-	0
	Ø	10		42.5	
ED ₅₀ (range)	0.2(0.1-0.2)				
ED ₉₀ (range)	0.3(0.2-0.3)				
	Resistance factor 90 1.0				
NS	0.1	5		-	96.5 ± 8.5
	0.3	5		-	87.8 ± 4.8
	1.0	5	1	-	5.1 ± 2.3
	3.0	5		-	0
	Ø	10		57.4	
ED ₅₀ (range)	0.4(0.2-0.6)				
ED ₉₀ (range)	0.8(0.3-1.1)				
	Resistance factor 90 2.7				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 15b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 225448AG
 or NUMBER BH 58522
 LON 1709..... PARASITE (SUB) SPECIES....P.berghei.....

Route of administration : s.c.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
RC	0.1	5		-	98.1 ± 7.5
	0.3	5		-	60.0 ± 8.4
	1.0	5	1	-	0
	3.0	5		-	0
	∅	10		4.1	
ED ₅₀ (range)	0.3(0.2-0.4)				
ED ₉₀ (range)	0.4(0.3-0.6)				
	Resistance factor ₁₉₀ 1.3				
P	0.1	5		-	82.7 ± 6.5
	0.3	5		-	66.4 ± 12.0
	1.0	5	1	-	21.2 ± 4.6
	3.0	5		-	1.3 ± 0.4
	∅	10		20.8	
ED ₅₀ (range)	0.3(0.2-0.7)				
ED ₉₀ (range)	1.2(0.8-2.4)				
	Resistance factor ₁₉₀ 4.0				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 15c

WR 225448 AG (BLOOD SCHIZONTOCIDES)
 BH 58522
 COMPOUND NAME LON 1709 P.berghei
 or NUMBER PARASITE (SUB) SPECIES.....
 Route of administration : S.C.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N/1100	0.1	5		-	68.0 \pm 7.7
	0.3	5		-	48.1 \pm 13.1
	1.0	5	1	-	0.1 \pm 0.1
	3.0	5		-	0
	\emptyset	10		23.0	
ED ₅₀ (range)	0.2 (0.1-0.4)				
ED ₉₀ (range)	0.4 (0.2-0.7)				
	Resistance factor ₁₉₀ 1.3				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistance factor ₁₉₀				

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TABLE 15d

WR 225448 AG

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME
or NUMBER

BH 58522

LON 1709

PARASITE (SUB) SPECIES... *P. berghei*.....

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.1	5		-	65.5 ± 19.2
	0.3	5		-	2.9 ± 0.8
	1.0	5	1	-	0.01 ± 0.01
	3.0	5		-	0
	∅	10		42.5	
ED ₅₀ (range)	0.1 (0.1-0.2)				
ED ₉₀ (range)	0.2 (0.2-0.3)				
	Resistance factors I 90 1.0				
NS	0.1	5		-	89.9 ± 4.2
	0.3	5		-	69.0 ± 4.7
	1.0	5	1	-	1.1 ± 0.4
	3.0	5		-	0
	∅	10		57.4	
ED ₅₀ (range)	0.3 (0.2-0.4)				
ED ₉₀ (range)	0.6 (0.4-1.0)				
	Resistance factor I 90 3.0				

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TABLE 15e

WR 225448AG

(BLOOD SCHIZONTOCIDES)

BH 58522

COMPOUND NAME
or NUMBER

LON 1709

PARASITE (SUB) SPECIES..... P.berghei

Route of administration : p.o.

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
RC	0.1	5		-	96.6 \pm 8.0
	0.3	5		-	60.0 \pm 10.8
	1.0	5	1	-	0.7 \pm 0.5
	3.0	5		-	0
	\emptyset	10		4.1	
ED ₅₀ (range)	0.3(0.2-0.4)				
ED ₉₀ (range)	0.6(0.4-0.8)				
	Resistance factor 190 3.0				
P	0.1	5		-	79.8 \pm 10.0
	0.3	5		-	51.9 \pm 11.1
	1.0	5	1	-	22.1 \pm 2.8
	3.0	5		-	1.0 \pm 0.4
	\emptyset	10		20.8	
ED ₅₀ (range)	0.3(0.2-0.5)				
ED ₉₀ (range)	1.2(0.6-1.9)				
	Resistance factor 190 6.0				

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TABLE 16a

WR 182232 AC

BE 08456

COMPOUND NAME
OR NUMBER

LIV/1307

PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H₂O

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 16b

WR 182232 AC

(BLOOD SCHIZONTOCIDES)

BE 08456

COMPOUND NAME LIV/1307

P.berghei

or NUMBER

PARASITE (SUB) SPECIES.....

FORMULATION_ Tween 80/H₂O Route of administration : po

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	3.0	5		-	50.9 \pm 5.2
	10.0	5		-	8.0 \pm 3.5
	30.0	5	1	-	0
	100.0	5		-	0
	Ø	10		17.4	
ED ₅₀ (range)	4.2 (3.1-5.4)				
ED ₉₀ (range)	7.8 (5.8-10.2)				
	Resistance factor I90				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor I90				

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TABLE 17a

WR 194343

(BLOOD SCHIZONTOCIDES)

BC 06452

COMPOUND NAME LIV/1354

or NUMBER

P.berghei

PARASITE (SUB) SPECIES.....

FORMULATION Tween 80/H₂O

Route of administration :

SC

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
N	3.0	5	-	-	20.5 \pm 4.7
	10.0	5	-	-	0.8 \pm 0.7
	30.0	5	1	-	0
	100.0	5	-	-	0
	ϕ	10	-	26.4	
ED ₅₀ (range)	1.5(1.1-2.4)				
ED ₉₀ (range)	4.2(2.3-5.3)				
	Resistance factor 190				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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TABLE 17b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME
or NUMBERWR 194343
BC 06452
LIV/1354PARASITE (SUB) SPECIES *P.berghei*

Route of administration : po

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 10
N	1.0	5		-	83.6 \pm 4.0
	3.0	5		-	69.9 \pm 4.2
	10.0	5	1	-	15.5 \pm 1.8
	30.0	5		-	0
	Ø	10		17.4	
ED ₅₀ (range)	3.9(1.6-6.2)				
ED ₉₀ (range)	7.6(3.2-12.2)				
	Resistance factor 190				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 18a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 215295
 or NUMBER BE 16378
 LIV/1381/LON 1722 PARASITE (SUB) SPECIES.....*P. berghei*.....

Route of administration : sc

FORMULATION Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	3.0	5		-	69.7 ± 2.9
	10.0	5		-	21.9 ± 5.1
	30.0	5	1	-	0.2 ± 0.1
	100.0	5		-	0
	Ø	10		26.4	
ED ₅₀ (range)	4.6(3.4-7.2)	100 = \approx LD ₄₀			
ED ₉₀ (range)	11.0(8.0-17.0)				
	Resistance factor 190				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 18b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 215295
 or NUMBER BE 16378
 LIV/1381/LON 1722.... PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : po

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	3.0	5		-	76.6 \pm 2.3
	10.0	5		-	31.3 \pm 5.7
	30.0	5	1	-	0.2 \pm 0.2
	100.0	5		-	0
	Ø	10		17.4	
ED ₅₀ (range)	5.6 (3.8-8.6)				
ED ₉₀ (range)	11.7 (8.0-18.2)				
	Resistance factor 190				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 19a

WR 216100 (BLOOD SCHIZONTOCIDES)
 BE 17491
 COMPOUND NAME LIV/1382
 or NUMBER PARASITE (SUB) SPECIES.....*P. berghei*.....

Route of administration : sc

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	3.0	5		-	33.3 ± 12.4
	10.0	5		-	2.2 ± 1.5
	30.0	5	1	-	0
	100.0	5		-	0
	Ø	10		26.4	
ED ₅₀ (range)	2.1(1.5-3.0)				
ED ₉₀ (range)	5.6(4.2-8.0)				
	Resistance factor 190				
ED ₅₀ (Range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 19b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME WR 216100
 or NUMBER BE 17491
 LIV/1382..... PARASITE (SUB) SPECIES.....P.bergbei.....

Route of administration : po

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
N	1.0	5		-	72.8 \pm 4.7
	3.0	5		-	57.8 \pm 2.8
	10.0	5	1	-	12.2 \pm 6.6
	30.0	5		-	0.01 \pm 0.01
	Ø	10		17.4	
ED ₅₀ (range)	2.6(1.4-5.4)				
ED ₉₀ (range)	6.1(3.4-12.8)				
	Resistance factor 190				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 20

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER WR 232143
 BH 01069
 LIV/1542 PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 10
N	3.0	5		-	88.6 ± 9.7
	10.0	5		-	84.1 ± 6.8
	30.0	5	1	-	43.2 ± 13.8
	100.0	5		-	0.5
	∅	10		26.4	
ED ₅₀ (range)	16.5(6.0-39.0)	100 = ~ LD ₄₀			
ED ₉₀ (range)	50.0(18-120)				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 21a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME
or NUMBER

Floxacrine.....

PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 10.
N	0.1	5		-	85.8 \pm 6.1
	0.3	5		-	76.2 \pm 2.1
	1.0	5	1	-	63.5 \pm 3.7
	3.0	5		-	6.2 \pm 2.1
	\emptyset	10		11.0	
ED ₅₀ (range)	0.7(0.2-1.6)				
ED ₉₀ (range)	3.0(1.2-7.4)				
	Resistance factor I90 1.0				
NS	0.1	5		-	54.9 \pm 3.4
	0.3	5		-	42.5 \pm 11.0
	1.0	5	1	-	12.4 \pm 8.8
	3.0	5		-	1.8 \pm 0.9
	\emptyset	10		11.3	
ED ₅₀ (range)	0.2(0.1-0.3)				
ED ₉₀ (range)	0.8(0.5-1.7)				
	Resistance factor I90 0.3				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 21b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME or NUMBER Floxacrine PARASITE (SUB) SPECIES P.berghei

FORMULATION: Tween 80/H₂O Route of administration : sc

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
N/1100	0.1	5		-	100 \pm 1.6
	0.3	5		-	52.9 \pm 8.6
	1.0	5	1	-	19.5 \pm 5.9
	3.0	5		-	4.9 \pm 2.3
	\emptyset	10		8.5	
ED ₅₀ (range)	0.7 (0.2-1.4)				
ED ₉₀ (range)	1.3 (0.5-2.8)				
	Resistance factor 190 0.4				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 22a

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME BK 02771
 or NUMBER LON/1752 PARASITE (SUB) SPECIES..... P.berghei

FORMULATION: Tween 80/H₂O
 Route of administration : sc

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
N	0.1	5	-	-	85.5 \pm 5.6
	0.3	5	-	-	77.5 \pm 3.0
	1.0	5	1	-	67.3 \pm 5.4
	3.0	5	-	-	59.1 \pm 5.8
	10.0	5	-	-	34.5 \pm 8.0
	Ø	10	-	11.0	
ED ₅₀ (range)	3.0(0.9- 8.0)	Interpolated graphically			
ED ₉₀ (range)	84.0(24 - >100)				
	Resistance factor I90 1.0				
NS	0.1	5		-	66.4 \pm 5.2
	0.3	5*		-	62.5 \pm
	1.0	5	1	-	57.3 \pm 2.5
	3.0	5		-	50.8 \pm 4.8
	10.0	5		-	17.2 \pm 3.4
	Ø	10		11.3	
ED ₅₀ (range)	1.0(0.2-4.0)	*2/5 died			
ED ₉₀ (range)	25.0(5.0-100)				
	Resistor factor I90 0.3				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 22b

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME BKO2771
 or NUMBER LON/1752
 PARASITE (SUB) SPECIES P.berghei
 SC

Route of administration :

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 100
N/1100	0.1	5		-	87.1 \pm 5.4
	0.3	5		-	72.5 \pm 6.1
	1.0	5	1	-	60.7 \pm 12.6
	3.0	5		-	47.5 \pm 4.3
	10.0	5		-	25.4 \pm 4.3
	\emptyset	10		8.5	
ED ₅₀ (range)	1.8(0.9-4.6)				
ED ₉₀ (range)	46.0(21 - >100)				
	Resistance factor I90 0.5				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor I90				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 23a

(BLOOD SCHIZONTOCIDES)

BK 02780
 LON/1753
 COMPOUND NAME
 or NUMBER PARASITE (SUB) SPECIES..... P.berghei
 FORMULATION: Tween 80/H₂O
 Route of administration : sc

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	0.1	5		-	84.0 \pm 3.1
	0.3	5		-	76.4 \pm 1.0
	1.0	5	1	-	66.4 \pm 3.5
	3.0	5		-	61.1 \pm 4.4
	10.0	5		-	55.8 \pm 5.2
	\emptyset	10		11.0	
ED ₅₀ (range)	41.5(4.4-90)				
ED ₉₀ (range)	> 100				
	Resistance factor 190				
NS	0.1	5		-	74.2 \pm 3.9
	0.3	5		-	70.4 \pm 4.2
	1.0	5	1	-	63.4 \pm 4.4
	3.0	5		-	53.3 \pm 2.4
	10.0	5		-	47.6 \pm 2.4
	\emptyset	10		11.3	
ED ₅₀ (range)	22.0(9.0-60)				
ED ₉₀ (range)	> 100				
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 23b

BK 02780
LON/1753

(BLOOD SCHIZONTOCIDES)

COMPOUND NAME
or NUMBER

PARASITE (SUB) SPECIES..... P.berghei

Route of administration : sc

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	Treated PR% Control PR% x 10
N/1100	0.1	5		-	98.8 \pm 3.8
	0.3	5		-	83.5 \pm 6.9
	1.0	5	1	-	65.4 \pm 5.7
	3.0	5		-	56.2 \pm 9.9
	10.0	5		-	51.1 \pm 9.0
	\emptyset	10		8.5	
ED ₅₀ (range)	3.5(1.3-16)				
ED ₉₀ (range)	48(18 - 100)				
	Resistance factor I90 36.9				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 23b

BK 02780

(BLOOD SCHIZONTOCIDES)

LON/1753

COMPOUND NAME
or NUMBER

PARASITE (SUB) SPECIES.....P.berghei.....

Route of administration : sc

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 10$
N/1100	0.1	5		-	98.8 \pm 3.8
	0.3	5		-	83.5 \pm 6.9
	1.0	5	1	-	65.4 \pm 5.7
	3.0	5		-	56.2 \pm 9.9
	10.0	5		-	51.1 \pm 9.0
	\emptyset	10		8.5	
ED ₅₀ (range)	3.5(1.3-16)				
ED ₉₀ (range)	48(18 - 100)				
	Resistance factor I90	36.9			
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF ANTIMALARIAL DRUG TEST

TABLE 24

WR 158124 (BLOOD SCHIZONTOCIDES)
 BD 22997
 COMPOUND NAME LON/1718
 or NUMBER PARASITE (SUB) SPECIES..... P.berghei

Route of administration : sc

FORMULATION: Tween 80/H₂O

Strain	Daily dose mg/kg DO - D+3	No. of Mice	No. of experiment	Mean control parasite rate %	$\frac{\text{Treated PR\%}}{\text{Control PR\%}} \times 100$
N	3.0	5		-	90.9 \pm 9.0
	10.0	5		-	78.0 \pm 11.9
	30.0	5	1	-	18.2 \pm 6.5
	100.0	5		-	1.4 \pm 0.7
	\emptyset	10		26.4	
ED ₅₀ (range)	13.5(7.0-34)				
ED ₉₀ (range)	42.0(22 - 110)				
	Resistance factor 190				
ED ₅₀ (range)					
ED ₉₀ (range)					
	Resistor factor 190				

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SUMMARY OF RESIDUAL ACTIVITY TESTS

TABLE 25

Dose = 30 mg/kg s.c. x 1

RESIDUAL ACTIVITY AT D+

LON	BN	WR No.	MFED	2	7	14	Type of Compound
1707	BG56327	194965 AG		+			Mannich base
1708	BJ30663	228258 AH		-			Mannich base
1709	BH58522	225448 AG		-			8-aminoquinoline
1715	AG99266	5990	30-60	-			8-aminoquinoline
1716	AJ63248	9792		-			
1717	AB65541	61112		-			Hydroxypyridine
1718	BD22997	158124		-			
1719	BE50003	181023	30-100	-			4-methyl primaquine
1720	BE17580	182234	3-10	-			2-methyl primaquine
1721	ZP12775	211814	1-3	-			8-aminoquinoline
1722	ZN43444	215295	300	-			8-aminoquinoline
1723	ZN81499	228000	10.30	-			8-aminoquinoline
1724	ZN78910	228583	30	-			8-aminoquinoline
1725	BH13989	233627		-			8-aminoquinoline
1726	BH35770	235485		-			8-aminoquinoline
1727	BH69990	238605		+			
1728	BJ08189	243789		-			
1729	BJ45691	246315		+			
1730	BJ51779	247705		±			
1731	BJ59202	248412		+			
1732	BH58120	237375		-			
1733	BG66798	228708	10-30	+			8-aminoquinoline
1734	BH89438	242511		+			
1736	BJ78592			-			
1740	AY29540			+			Quinolone/Naphthoquinone
1741	BC78878			+			
1751	ZN41968			-			
1752	BKO2771			+++	++	+	Floxacrine analogue
1753	BKO2780			-			Floxacrine analogue

± Residual Activity

- No Residual Activity

+ Slight Residual Activity

++ Marked Residual Activity

+++ Fully Residual Activity

TABLE 26

SUMMARY OF RESIDUAL ACTIVITY TEST

Dose = 100 mg/kg sc

RESIDUAL ACTIVITY AT D+

LON	BN	WR No.	MFED	2	7	14	Type of Compound
1707	BG56327	194965 AG		++	++		Mannich base
1727	BH69990	238605		++	-		
1729	BJ45691	246315		++***	-**		
1730	BJ51779	247705		MTD	MTD		
1731	BJ59202	248412		+	-		
1734	BH89438	242511		++**	-***		Quinoline/Naphthoquinone
1740	AY29540			+	-		
1741	BC78878			+	-		

* 2/5 DIED

** 3/5 DIED

*** 4/5 DIED

SUMMARY OF RESULTS OF RAT TEST FOR ACTIVITY AGAINST
EXOERYTHROCYTIC STAGES

COMPOUND : WR225448 (Lon 1709) ROUTE : sc x 1
 VERTEBRATE HOST: Albino rats (body weight = 60g)
 INVERTEBRATE
 HOST: A.stephensi (50-100 mosquitoes/rat)
 PARASITE: P.y.nigeriensis
 TREATED: 1 hour post infection

Dose mg/kg	Schizonts in biopsy at + 45 hours	Blood films				
		D+3	D+4	D+6	D+8	D+9
Ø	10-20/section. all large	+				+
0.25	13-18/section. Variable in size	+			+	
1.0	0-24 /section. Very variable in size	+			-	
3.0	0-1/section. Very small, abnormal	-	-	+		+
5.0	0 seen	-	-	+	+	
10.0	0 seen	-	-	-	-	-
30.0	0 seen	-	-	-	-	-

Fig. 1

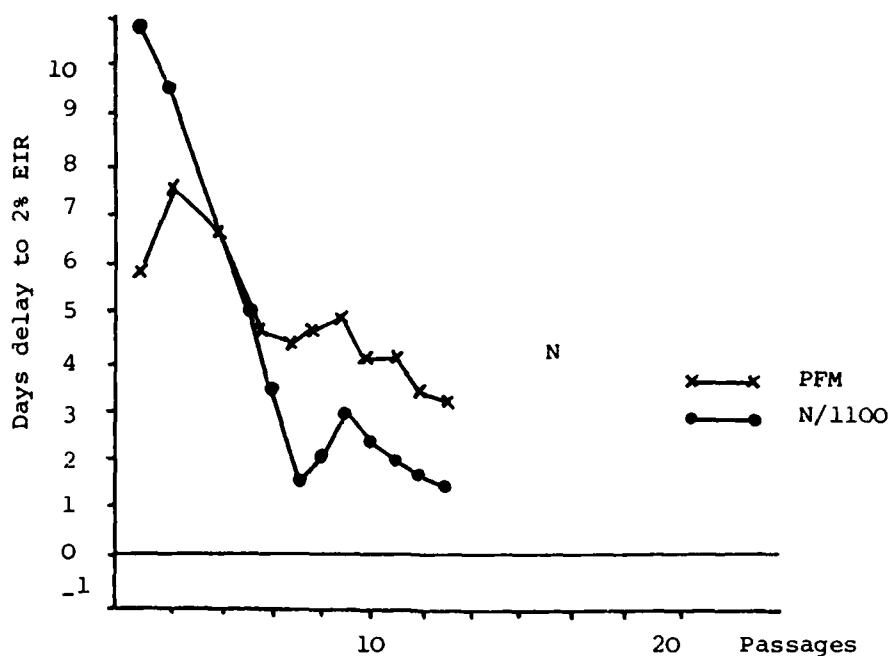


Fig. 1a. Development of resistance in drug sensitive P.berghei (N strain) to mefloquine alone (N/1100) and mefloquine administered together Fansidar (PFM) using the relapse technique.

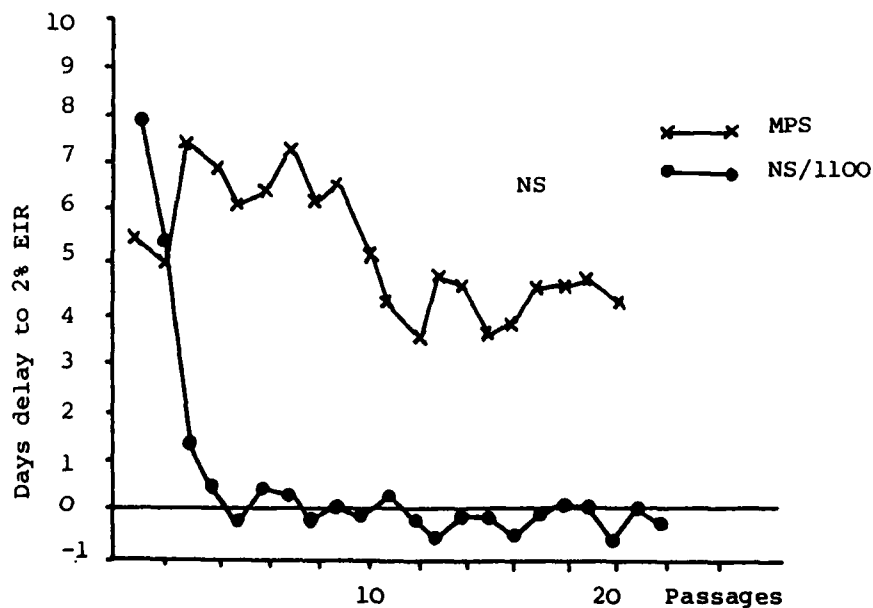


Fig. 1b. Development of resistance in chloroquine-resistant P.berghei (NS strain) to mefloquine alone (NS/1100) and to mefloquine administered together with Fansidar (MPS) using the relapse technique.



Plate 1. Effect of WR 194965 on blood stage of P.berghei (N strain) 3 hours post treatment with a single dose of 10 mg/kg sc. (x 52000)

Note swelling of digestive vacuoles and release of pigment into cytoplasm.

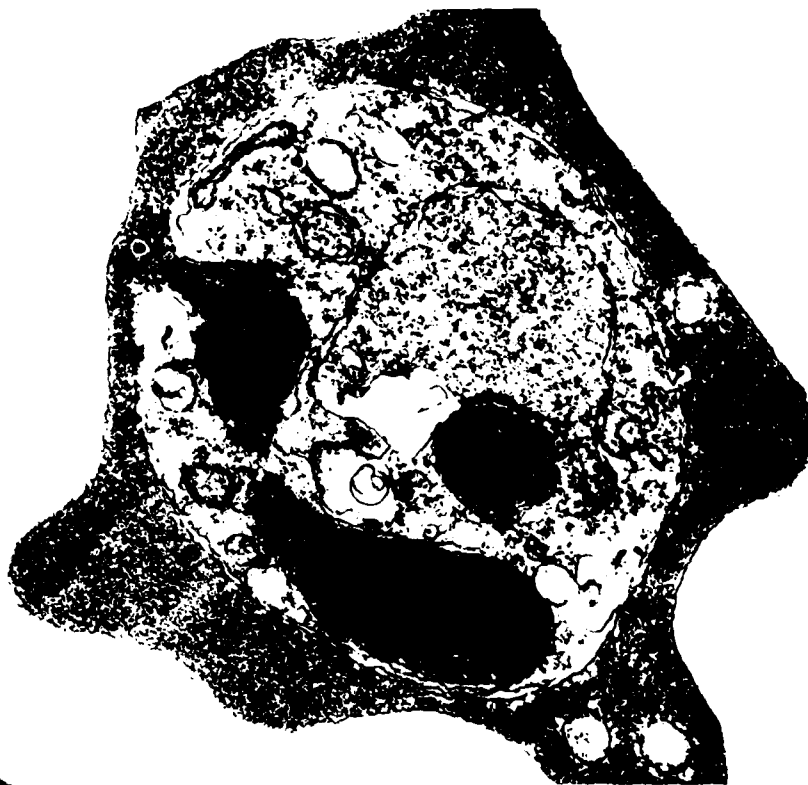


Plate 2. Effect of WR228258 on blood stage of P.berghei (N strain) 1 hour after treatment with a single dose of 10 mg/kg sc (x 26000)

Note nuclear blebbing and generalised membrane damage at 1 hour.

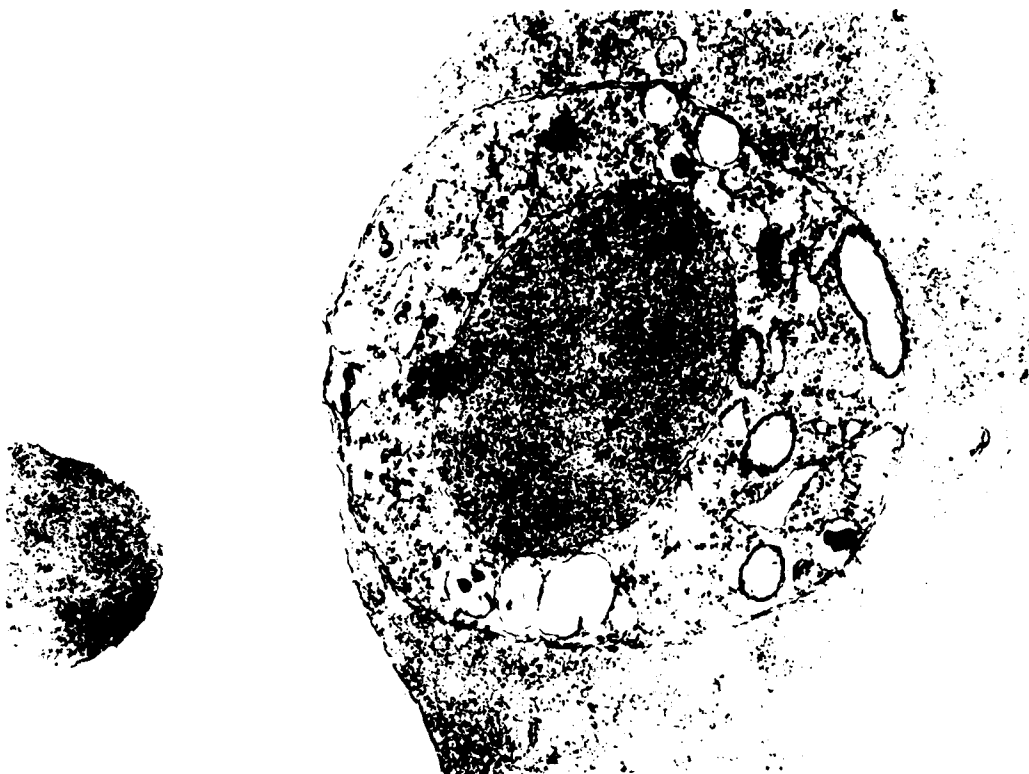


Plate 3. Effect of WR 225448 on blood stage of P.berghei (N strain) 24 hours after treatment with a single dose of 10 mg/kg sc. (x 26000)

Note the marked proliferation of mitochondria

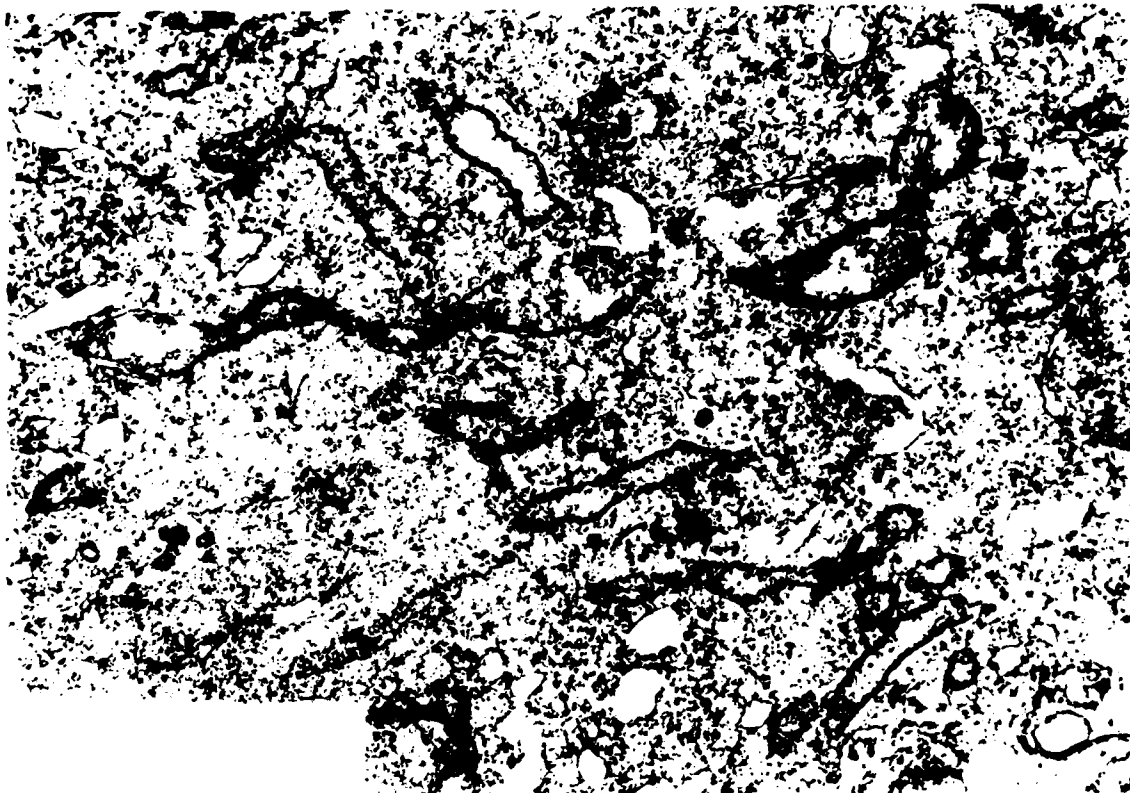


Plate 4. 45 hour exoerythrocytic schizont of P.y. nigeriensis in rat liver showing the effect of a single sc. dose of 50 mg/kg primaquine administered 3 hours after infection. (x 26000)

Note the thickening and darkening of mitochondrial membranes and early pathology of these organelles

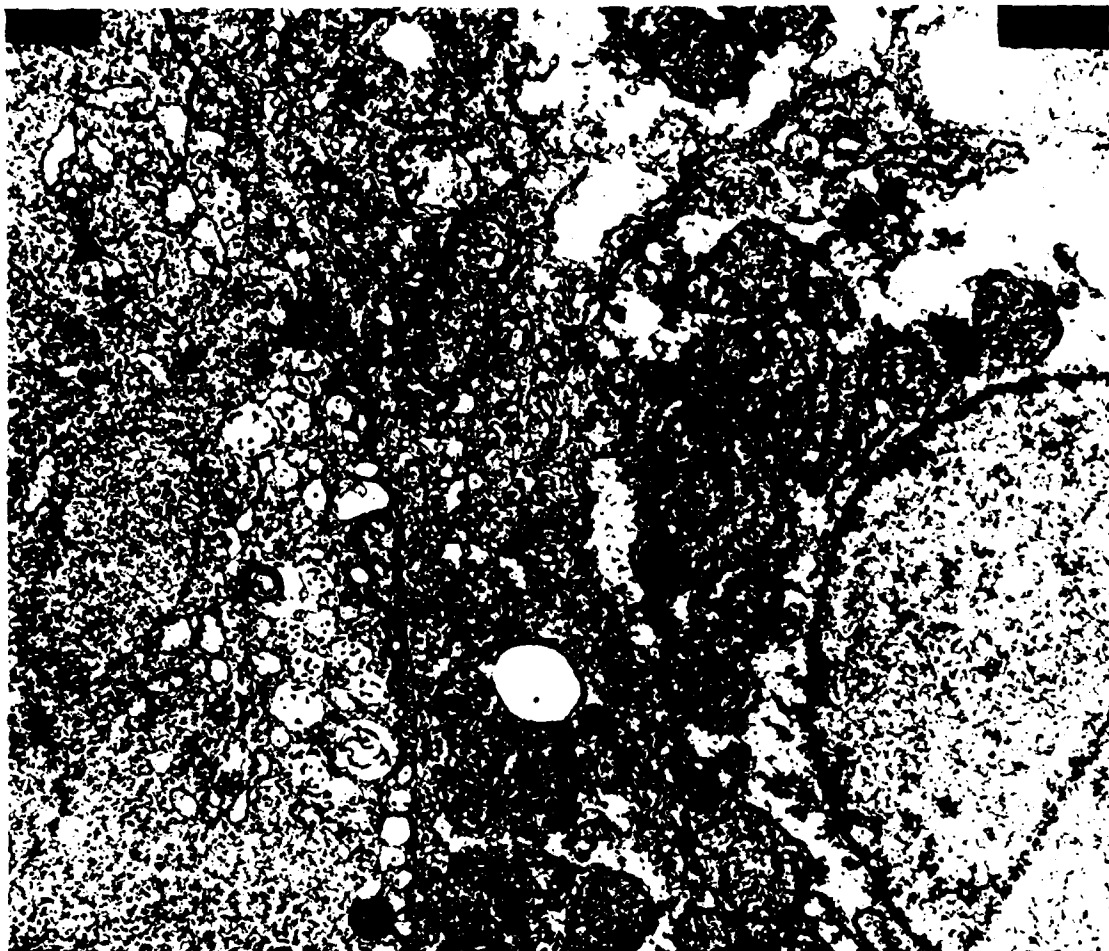


Plate 5. 45 hour exoerythrocytic schizont of P.y.nigeriensis showing the effect of a single sc. dose of _____ mg/kg WR 225448.

Note that the "enzyme" particles are no longer breaking out of the parasite membrane to act on host cell. The drug has apparently stopped completely this normal parasite activity. The outer parasite membrane is here straight and without bursting "enzyme" vacuoles.